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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,387	12/08/2003	Francis J. Giles	PHARMA-139	8138

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,387	GILES ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9,10,14,15,17-22,25-32 and 39-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,9,10,14,15,17-22,25-32,39-45,48 and 51-62* is/are rejected.

7)☒ Claim(s) *46,47,49 and 50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 9/20/2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In view of the new rejections being applied against the instant claims, the finality of the prior Office Action is hereby **withdrawn**.

Status of the Claims

Claims 1, 7, 9-10, 14-15, 17-22, 25-32 and 39-62 are currently pending and are the subject of this Office Action. This is a Non-Final Office Action.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17, 19-22, 27-30, 39-43, 48, 51-53, 55 and 57-62 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the synergistic treatment of chronic myeloid leukemia or other leukemia that express BCR-ABL, does not reasonably provide enablement for the *synergistic* treatment of all leukemia. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the instant case, applicants have demonstrated synergistic results for the treatment of chronic myeloid leukemia with troxacitabine and imatinib mesylate (see pages 24-27 of specification). However, it is not clear from the specification that such a synergistic effect will be observed if the leukemia being treated is BCR-ABL-negative. For example, Topaly *et al.*, cited for evidentiary purposes, discloses that many chemotherapeutics demonstrate synergism with imatinib mesylate when administered to BCR-ABL-positive leukemia such as CML (Abstract). However, no synergism is observed when the leukemia cell line does not express BCR-ABL (Figure 4).

As such, applicants have not demonstrated or provided any guidance on how the skilled artisan can synergistically treat a BCR-ABL-negative leukemia with the claimed combination of troxacitabine and imatinib mesylate. Topaly *et al.* makes it clear that the synergistic effect of chemotherapeutics combined with imatinib mesylate is not seen in BCR-ABL-negative leukemia cell lines.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 7, 9-10, 14-15, 18-19, 25-27, 30-32, 39-41, 43-45, 52, 54-57 and 60-62 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/07413 (prior art of record), Giles *et al.* (JCO, 2001 – prior art of record) and Druker *et al.* (N. Engl. J. Med., 2001, vol. 344, pages 1038-1042) in view of Fang *et al.* (Blood, 2000, vol. 96, pages 2246-2253) and Topaly *et al.* (prior art of record).

The instant claims are drawn to compositions comprising L-(-)-OddC (troxacitabine) and imatinib mesylate (STI571) and methods of treating leukemia with said compositions. Please note that this rejection only applies to claims drawn to the obviousness of the claimed pharmaceutical compositions and to the obviousness of methods of treating CML or other leukemias that are BCR-ABL-positive.

Troxacitabine is well known in the art as a treatment for leukemia and is preferably used as its (-) enantiomer. For example, WO discloses the use of (-)-(*2S,4S*)-L-(2-hydroxymethyl-1,3-dioxolan-4-yl)cytosine (also referred to as (-)-OddC, L-OddC, or (-)-L-OddC) in the treatment of cancer (page 5, lines 17-27; page 47, Claim 12). The compound is administered as its substantially (-) enantiomer (*i.e.* free of the (+) enantiomer) (page 6, lines 6-11). WO defines "enantiomerically enriched" to refer to a nucleoside composition that includes at least approximately 95%, and preferably approximately 97%, 98%, 99%, or 100% of a single enantiomer of that nucleoside. In a preferred embodiment, (-)-L-OddC or its derivative or salt is

provided in a nucleoside composition that consists essentially of one enantiomer, *i.e.*, as the indicated enantiomer (the L-enantiomer) and substantially in the absence of its corresponding D-enantiomer (*i.e.*, in enantiomerically enriched, including enantiomerically pure form) (page 11, lines 6-18).

Leukemia is recited as one type of cancer (-)-L-OddC can be used to treat (page 6, lines 22-28). It is further disclosed that (-)-L-OddC can be administered in combination with other anticancer agents, including interferons, interleukins and cytarabine (page 7, line 21 to page 8, line 20). Figure 3 shows the results of treatment of P388 (an experimental lymphocytic leukemia cell line) leukemic mice with (-)-L-OddC. Further, the *in vitro* activity of (-)-L-OddC was demonstrated against several different leukemia cell lines (Table 2, page 35).[1] These tested leukemia cell lines correspond to an acute lymphoblastic cell line (CCRF-CEM), an acute promyelocytic leukemia cell line (HL-60), a chronic myelogenous leukemia (CML) cell line (K-562) and an acute lymphoblastic leukemia cell line (MOLT-4).

Giles *et al.* is provided to show that the instantly claimed doses of (-)-L-OddC for the treatment of leukemia were known in the art. (-)-L-OddC (troxacitabine) is disclosed as being effective in the treatment of refractory or relapsed acute myeloid leukemia (AML) or lyphocytic (ALL) leukemia, myelodysplastic syndromes (MDS) or chronic myelogenous leukemia in blastic phase (CML-BP) (see especially Abstract). Troxacitabine was administered to patients in doses of 0.72 to 10 mg/m^2/day (page 765, Table 3). The MTD was determined to be 8 mg/m^2/day (Abstract).

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[1] It is noted that the leukemia cell lines in Table 2 are not properly identified. It is believed that RL-60(TB) is HL-60; BSOLT-4 is MOLT-4; and RPMI-2.26 is RPMI-82.26.

Druker *et al.* is provided to show that the instantly claimed doses of imatinib mesylate (STI571) for the treatment of leukemia were known in the art. STI571 is a specific inhibitor of the BCR-ABL tyrosine kinase and has been used to treat CML in blast crisis as well as ALL with the Philadelphia chromosome (*i.e.* ALL expressing BCR-ABL) (see especially Abstract). BCR-ABL is present in virtually all cases of CML and in 20% of cases of ALL. STI571 was given orally at daily doses ranging from 300 to 1000 mg (Abstract; page 1040, Tables 4 & 5).[2]

Neither WO, Giles *et al.* nor Druker *et al.* disclose a combination of troxacitabine and imatinib mesylate, although WO does suggest that (-)-L-OddC can be combined with other chemotherapeutic agents (page 7, line 21 to page 8, line 20).

However, Fang *et al.* and Topaly *et al.* disclose that combined therapies comprising STI571 and other antileukemic drugs are synergistic when used to treat BCR-ABL-positive human leukemia. For example, Fang *et al.* disclose that STI571 induces hemoglobin levels and apoptosis of K562 and HL-60/Bcr-Abl leukemia cells (page 2249, right column). Cotreatment with STI571 significantly increased the percentage of apoptotic cells following exposure to Ara-C or doxorubicin (Table 2). This effect was not observed in HL-60/neo cells, which do not express BCR-ABL and are highly sensitive to apoptosis induced by Ara-C and doxorubicin (page 2251, left column). As conventional chemotherapy with Ara-C, doxorubicin and etoposide does not have major clinical efficacy against BCR-ABL-positive acute leukemia or the blast crisis of CML, the data presented suggest that the effects of STI571 on these leukemias "may

[2] The average male has a body surface area of 1.9 m^2, the average female, 1.6 m^2. Thus, the doses administered correspond to 0.16 g/m^2 to 0.53 $g/m^2/d$ (males) and 0.19 g/m^2 to 0.63 $g/m^2/d$ (females).

sensitize BCR-ABL-positive human leukemic cells to apoptosis induced by antileukemic drugs" (page 2252, right column, last paragraph).

Further evidence of such synergism is found in Topaly *et al.* wherein STI571 is demonstrated to have a synergistic effect when administered with other chemotherapeutic drugs on BCR-ABL-positive CML cells (Abstract; Figure 2). The data provided therein implies that:

> "STI571 exhibits strong synergism with apoptosis-inducing cytarabine, mafosfamide and etoposide at higher levels of growth inhibition, which may originate from increasing inhibition of the BCR-ABL tyrosine kinase with subsequent induction of apoptotic pathways by these chemotherapeutic drugs" (page 346, right column).

Thus, the reference provides one skilled in the art with the motivation and reasonable expectation of success in treating BCR-ABL-positive CML with a combination therapy of STI571 and other chemotherapeutic agents.

The instantly claimed formulations and methods of treating CML with a synergistic combination of (-)-L-OddC and imatinib mesylate would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The prior art discloses that both of these agents can be used to treat leukemia in the doses instantly claimed and further demonstrates that STI571 has a synergistic effect when combined with other chemotherapeutic agents in the treatment of CML. As such, the skilled artisan has been provided with the explicit teaching that STI-571 can be combined with other chemotherapeutics and would be imbued with

more than a reason expectation that such a combination would be synergistic in the treatment of CML or other leukemias wherein BCR-ABL is expressed (*e.g.* ALL).

The motivation to combine the above references is explicitly found in Fang and Topaly as stated above. Moreover, (-)-L-OddC and STI571 (*i.e.* imatinib mesylate) are individually known in the art as agents for treating leukemia, whose efficacy when administered alone is well established for the treatment of different leukemia types. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15, 17-22, 26-30, 41-43 and 52-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 10-16 and 22-31 of U.S. Patent No. 6,645,972. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant method claims and the claims of '972 are drawn to the treatment of resistant and refractory leukemia including AML and CML with (-)-L-OddC. The comprising language of '972 allows for the inclusion of another chemotherapeutic, including the instantly claimed imatinib mesylate (*e.g.* Claim 25 of '927).

Allowable Subject Matter

Claims 46-47 and 49-50 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the

base claim and any intervening claims. The prior art does not teach or fairly suggest the claimed ratios of (-)-L-OddC to imatinib mesylate.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

September 28, 2006

Ardin H. Marschel 9/29/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER